EXHIBIT E

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO WAVE 5**	**Master File No. 2:12-MD-02327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

RULE 26 EXPERT REPORT OF DANIEL ELLIOTT, M.D.

I. Background and Qualifications

I am an Associate Professor of Urology at Mayo Graduate School of Medicine in Rochester, Minnesota. I received an M.D. in 1993 from Loma Linda University School of Medicine in Loma Linda, California. Following graduation from medical school, I completed my surgical residency in Urology at the Mayo Graduate School of Medicine at the Mayo Clinic in 1999. I completed a one-year advanced surgical fellowship at Baylor College of Medicine in Houston, Texas, in Neurourology, Urodynamics, and Voiding Dysfunction. I then re-joined the faculty at the Mayo Clinic, where I have spent the last 15 years specializing in treatment for pelvic organ prolapse and urinary incontinence in women, as well as urinary incontinence in men. I have published over 60 peer-reviewed articles and given more than 100 hundred lectures, many of which relate to urinary incontinence and pelvic organ prolapse. A Mayo Clinic colleague and I were the first to perform robotic sacrocolpopexy surgery for the treatment of high-grade prolapse and the first to publish extensively on the subject. I have also published multiple scientific manuscripts concerning polypropylene meshes in the animal

model. I am a frequent invited lecturer at medical and surgical conferences addressing pelvic organ prolapse and stress urinary incontinence and their evaluation, treatments, surgical options, and management of complications. I recently passed the subspecialty credentialing process for Female Pelvic Medicine and Reconstructive Surgery, established by the combined boards of the American Board of Urology and the American Board of Obstetrics and Gynecology. Attached as Exhibit "A" to this report is a copy of my current curriculum vitae, which includes an up-to-date list of my publications, presentations, awards, and other academic activities, as well as my fee schedule. My recent trial testimony is listed in Exhibit "B."

II. Bases of Opinions

I have been asked to provide opinions regarding the subject of female stress urinary incontinence, its evaluation, treatments, surgical options and management of complications as well as to address the actions of Ethicon, Inc., Ethicon Women's Health and Urology, a Division of Ethicon, Inc., Gynecare and Johnson & Johnson (collectively referred to as Ethicon). The focus of my investigation for this report is on the TVT-Secur System ("TVT-S") and, specifically, the characteristics of the product that make it defective or, in other words, that make the risks to the patient outweigh the benefits to the patients. My opinions are based on my personal knowledge, experience, and my investigation in this case. All of my opinions, and the bases of those opinions, are true and correct to the best of my knowledge and belief, including those related to scientific and medical issues, which I believe to be true and correct to a reasonable degree of scientific and medical certainty. I do, however, reserve the right to supplement this report and my opinions in light of any additional material or information provided to me, including any reports submitted and/or any other discovery that is taken in this

case. Furthermore, if called to testify, I would plan to use various demonstrative exhibits, animations, video recordings, and/or anatomic models to show the relevant anatomy and surgical procedures and to describe my opinions as set forth in this report.

My opinions and conclusions regarding the TVT-S, its surgical procedure, its impact on patients and surgical colleagues, as covered throughout this report, have not been derived in isolation or from solitary data and opinion; rather, my report has been formed and influenced by multiple sources, briefly summarized as follows: my independent clinical and laboratory mesh- specific research, including clinical manuscripts pertaining to female stress urinary incontinence ("SUI"), female pelvic organ prolapse ("POP"), including mesh-specific complications; animal laboratory studies regarding the effects of polypropylene mesh and host foreign body response and inflammatory response; advanced surgical fellowship training in Voiding Dysfunction and Neurourology, which is above and beyond the normal six-year urologic surgical training; my personal surgical, clinical, and research experience implanting Prolene mesh slings; my personal surgical, clinical, and research experience as a Female Pelvic Medicine and Reconstructive surgical specialist at a high-volume tertiary center managing highly complicated SUI patients and mesh-related complications, including medical and surgical revisions and removal and treatment of synthetic mesh slings, including complications caused by the TVT-S device; my attendance and participation at national and international Urological and Gynecological surgical meetings, including but not limited to the International Pelvic Pain Society, International Continence Society, Society of Female Urology and Urodynamics, American Urologic Association, Canadian Urological Association, Mayo Clinic Urology Review, UCLA State of the Art Urology, European Urological Association Subsection of Female Urology and Subsection of Reconstructive Urology. I have

prepared and given lectures at national and international meeting specifically focused on the complexities of treating female SUI and the management of complications associated with such treatments, including but not limited to the International Continence Society meeting, Society of Female Urology and Urodynamics meeting, American Urologic Association meeting, Canadian Urological Association meeting, UCLA State of the Art Urology meeting, and European Urological Association Subsection of Female Urology and Reconstructive Urology meeting. I have had personal interactions and discussions with national and international urologic, gynecologic, urogynecologic, and general surgery colleagues regarding the management of SUI in women, manifestation of mesh-specific complications, and the treatment of mesh-specific complications. As part of my interest in being as educated and as up-to-date and accurate as possible, I have reviewed the readily available medical literature pertaining to the treatment of SUI and the management of its complications from sources including but not limited to medical journals, the United States National Library of Medicine, and the National Institute of Health.

I am a surgical journal editor and/or reviewer for 14 urologic and/or gynecologic journals (please see Curriculum Vitae for complete listing of journals) and was named Best Reviewer in Female Urology/Incontinence/Neurourology for two consecutive years (2012-2013) for the Journal of Urology. This is the highest honor awarded by the Editor of the Journal of Urology for excellence in manuscript review and preparation.

I have also performed a systematic review of internal Ethicon documents as they pertain to surgical mesh, TVT-S, the TVT-S procedure, expected SUI surgical results, expected SUI complications and rates of SUI complications, and marketing strategies designed for my surgical colleagues in urology, gynecology and urogynecology, as well as for potential SUI

patients. I have also reviewed the testimony of Ethicon employees. All materials I reviewed or relied on in support of my findings and opinions are included throughout this report and/or listed in Exhibit "C."

III. Summary of Opinions

A. ***Background on SUI and Treatments***

1. Stress Urinary Incontinence
2. Alternative/Traditional SUI Treatment Options
   a. *Non-surgical*
   b. *Surgical*

B. ***The Polypropylene Mesh in the TVT-S Should Not Be Used in the Pelvic Floor Due to Known Complications and Hazards***

1. Polypropylene mesh in the TVT-S is not inert and degrades
2. The MSDS for the Prolene mesh states not to use with strong oxiders like peroxides, which can be abundantly found in the vagina
3. The TVT-S mesh is heavy with small pores, causing increased tissue response, chronic inflammatory response, contraction and shrinkage of the mesh, fibrotic bridging and scar plate formation
4. Ethicon's Prolene mesh tested positive for cytotoxicity

C. ***The TVT-S Should Not Be Used in the Pelvic Floor Due to its Defective Design***

1. The TVT-S mesh is laser cut, resulting in a stiffer product and higher incidence of complications
2. The TVT-S design is flawed because there is no way to properly tension the device
3. The TVT-S is defectively designed in its insertion instruments and technique
4. Ethicon had several preferred alternatives to the TVT-S available

D. ***Ethicon Failed to Disclose and/or Downplayed Adverse Risks, Complications, and Product Information in its Instructions for Use ("IFU") and Patient Brochures***

E. ***Ethicon Failed to Provide Adequate Training for Surgeons Using the TVT-S***

IV. Expert Opinions

A. ***Background on SUI and Treatments***

1. Stress Urinary Incontinence

Female stress urinary incontinence ("SUI") is a relatively common condition in which a woman leaks urine when her body experiences an increase in abdominal pressure, which in turn increases the pressure on the bladder. The abdominal pressure (A.K.A. "stress") is caused by a wide variety of activities including coughing, laughing, sneezing, jumping, bending over, picking something up, running, or any other sudden movement that increases pressure on the bladder.

In a woman, the urine leakage often results from weakening of the muscles that surround the urethra and/or a lack of fascial support for the urethra. The fascia below the urethra serves as a sort of net to prevent the urethra from falling. SUI is much more common in women than in men, largely because of pregnancy, childbirth, menopause and hysterectomies, among other factors. Each of these conditions cause physical changes in the fascia used to support the urethra, which in turn results or contributes to SUI. There are multiple fascias, or tissues, that support the urethra, including fascia located in the area of the pelvic floor and endopelvic fascia. In a woman with SUI, these fascia fail to provide sufficient support for the urethra, allowing the urethra to move downward when there is a sudden increase in pressure, such as that caused by a cough or a sneeze. When this happens, urine leaks out of the urethra. Some SUI can also be linked to intrinsic sphincter deficiency ("ISD"), a condition in which the urinary sphincter is weakened.

SUI can have very serious effects on a woman's physical and mental health. It is not uncommon for women with SUI to stop participating in activities they once enjoyed, such as sports and other recreational activities, or to experience mental illness such as depression.

2. Alternative/Traditional SUI Treatment Options

a. *Non-surgical*

SUI presents in 15% to 35% of women.[1] Although some surgical treatments are typically safe and highly effective, many patients wish to avoid surgery for a variety of reasons. Regardless of the patient's willingness to commit to surgery, in most cases, it is recommended that non-surgical options be implemented first.[2]

Behavior modification & Pelvic Floor Therapy & Exercises

Simple lifestyle or behavioral modifications such as weight loss and/or avoidance of dietary irritants like caffeine and nicotine are often the first line of treatment. In many cases those options may be the only treatment necessary. Additionally, pelvic floor muscle exercises (Kegel exercises) are used to strengthen the muscles surrounding the urethra so that urine is less likely to leak. These therapies require time, effort, and commitment, but they do not have side effects and are often very effective.

Alternatively, pelvic floor electrical stimulation combined with biofeedback may prove useful. Pelvic floor electrical stimulation utilizes electrical current to strengthen the pelvic floor and improve its function. Biofeedback is a treatment regimen performed under the care of a specialist and/or physical therapist. It is a safe and effective method of increasing pelvic floor strength and has a role in helping women with mild stress incontinence. Biofeedback

[1]Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, van Kerrebroeck P, Victor A, Wein A, Standardisation Sub-committee of the International Continence Society Neurourol Urodyn. 2002; 21(2):167-78. Milsom I, Altman D, Lapitan MC, Nelson R, Sillen U, Thom D. Epidemiology of urinary (UI) and Faecal (FI) Incontinence and Pelvic Organ Prolapse. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence; 4th International Consultation on Incontinence; Paris: Health Publication Ltd; 2009. pp. 35–111.

[2] Hay-Smith J, Berghmans B, Burgio K, et al. Adult Conservative Management. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. Incontinence; 4th International Consultation on Incontinence; Paris: Health Publication Ltd; 2009. pp. 1025–1120

attempts to retrain patients on how to more appropriately use their pelvic floor muscles, thereby improving their urine control. Consequently, the patient becomes more aware of her pelvic muscles and is better able to identify and use them.

Medication

There are several medications that have been studied for the potential treatment of SUI (Topical Estrogen, α-Adrenergic Agonists, Imipramine, Duloxetine, β-Adrenergic Antagonists, and β-Adrenergic Agonists). However, to date their benefit is minimal for SUI and is essentially limited to possibly benefiting overactive bladder.

Pessaries

Pessaries have been used for thousands of years to treat POP and SUI and, prior to the advent of successful surgical options, pessaries were essentially the only viable treatment for POP and SUI. Specifically, "continence pessaries" represent an alternative or complementary non-surgical approach to the treatment of SUI. These devices work by providing a platform against which the urethra can compress during strenuous activity such as lifting or coughing. There are several studies describing the effectiveness of pessaries for treatment of SUI, but most of these studies are based on small samples of participants with short-term follow-up, which make the results questionable. Ultimately, however, due to inherent limitations of effectiveness complications such as vaginal pain, discharge, and odor, and the necessity of routine medical care, most patients with SUI discontinue using the pessary at some point.

b. *Surgical*

Surgeons have spent hundreds of years trying to develop successful treatments for SUI. Over time, several successful surgical techniques have been devised, but all of the treatments have the common component of reestablishing support for the urethra that has been weakened and damaged by childbirth, hysterectomy, obesity, and/or age.

Marshall-Marchetti-Krantz & Burch Colposuspension

In the 1940's, the Marshall-Marchetti-Krantz ("MMK") procedure was developed. The MMK procedure is a surgery in which the surgeon secures the neck of the bladder—i.e., where the bladder meets the urethra—to the pubic bone with a series of sutures. The Burch colposuspension procedure was developed shortly after the MMK procedure. The Burch procedure is successful in treating urinary incontinence with success rates equivalent to mid-uretheral synthetic slings. Although the Burch procedure takes longer than a procedure to implant a synthetic mid-uretheral sling, the long-term complications with Burch, particularly relating to chronic pain and dyspareunia, are minimal when compared to the complications arising from mid-uretheral synthetic slings.

Pubovaginal Slings (Autologous/Cadaveric)

In the 1980's, a major advancement occurred with the introduction of a procedure known as the pubovaginal sling (PVS). The PVS procedure uses harvested tissue from the tough abdominal wall, called abdominal fascia. That tissue is then implanted in the shape of a hammock-like sling around the neck of the bladder and up to the abdominal wall. Since the fascial tissue comes from the patient herself, it is called "autologous," meaning tissue that comes from the same individual. The procedure rapidly rivaled the Burch colposuspension as the "gold standard" for the treatment of SUI in women.

With the advent of biologic and synthetic mesh slings, the number of traditional PVS procedures initially decreased. However, with the increasing awareness among surgeons and patients regarding the complications of vaginal synthetic mesh (including but not limited to permanent dyspareunia, life-altering pain, chronic sexual dysfunction, lifetime erosion risk, and others listed throughout this report), the PVS procedure has seen a significant

resurgence. In some regions and practices around the nation, the PVS has become the mainstay of therapy. In my own practice at a major tertiary referral medical center, I have abandoned essentially all synthetic mesh sling implantation due primarily to those complications mentioned above.

Synthetic Mesh in General Surgery

Abdominal and thoracic wall weaknesses (hernias) develop due to conditions such as birth defects, surgical complications, and radiation effects. Traditional hernia repair surgery evolved using sutures (stitches) to bring native tissue together. However, due to the inherent weaknesses of the tissues, failure was common and frequently resulted in significant pain and suffering for the patient. As a result, surgical meshes for hernia repairs were introduced in the 1950's. Since then, academic presentations, surgical reports, and journal manuscripts have described mesh- related complications such as chronic pain, abdominal wall rigidity, mesh contraction, infection, fistula formation, chronic inflammatory process, and weakness recurrence.[3]

[3] Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan; 2(1):103-17. Agresta F, Baldazzi G, Ciardo et al: Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone for TAPP inguinal hernia repair. Surg Laparosc Endosc Percutan tech 2007, 17; 91- 94. Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia (1997)1:15-21. Bellon J, Honduvilla N, Jurado F et al: In vitro interaction of bacteria with polypropylene/ePTFE prostheses. Biomaterials. 2001 Jul; 22(14):2021-4. Bouikerrou M, Boulanger L, Rubod C et al: Study of the biomechanical properties of synthetic implanted in vivo. European J. Obstet & Gynecol and Repro Bio 134: (2007)262-267. Klinge U, Klosterhalfen M, Muller A et al: Shrinking of polypropylene mesh in vivo: an experiment study in dogs. European Journal of Surgery Volume 164, Issue 12, pages 965–969, December 1998. Klinge U, Klosterhalfen B, Muller M et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg. 1999 Jul; 165(7):665-73. Klinge U, Klosterhalfen B, Birkenhauer V: Impact of polymer pore size on the interface scar formation in a rat model. J. Surgical Research 103, 208-214 (2002). Klosterhalfen B, Klinge W, Schumpelick V: Functional and morphological evaluation of different polypropylene- mesh modifications for abdominal wall repair. Biomaterials. 1998 Dec; 19(24):2235-46. 13 Krause H, Galloway S, Khoo S et al: Biocompatible properties of surgical mesh using an animal model. Aust N Z J Obstet Gynaecol. 2006 Feb; 46(1):42-5. Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan; 22(1):47-52. Garcia M, Ruiz V, Godoy A, et al: Differences in polypropylene shrinkage depending on mesh position in an experimental study. American Journal of Surgery Vol 193, Issue 4, April 2007, p538-542. Cappelletti M, Attolini G, Cangioni G, et al. The use of mesh in abdominal wall defects. Minerva Chir. 1997 Oct; 52(10):1169-76. Klosterhalfen B, Klinge W, Hermanns B et al: Pathology of traditional surgical nets for hernia repair after long- term implantation in humans. [ABSTRACT] Chirugr 2000; 71:43-51. Seker D, Kulacoglu H. Long-term complications of mesh repairs for abdominal wall hernias. J Long Term Eff Med Implants. 2011; 21(3):205-18. Cobb W, Burns J, Peindl R et al: Textile analysis of heavyweight, mid-weight, and lightweight polypropylene mesh in a porcine ventral hernia model. J Surgical Research 136, 1-7 (2006). Pandit A, Henry J. Design of surgical meshes - an engineering perspective. Technol Health Care. 2004; 12(1):51- 65. Pierce L, Grunlan M, Hou Y et al: Biomechanical properties of synthetic and biologic graft materials following long-term implantation in the rabbit abdomen

An abundance of evidence in medical literature and basic scientific data has been accumulated over the past two decades and indicates a strong and direct relationship between postoperative mesh complications and mesh design.[4] Reducing mesh-related complications demands a thorough understanding and knowledge of the chemical, physical, and synthetic characteristics of meshes and how they react inside the human body. At this point, there is a scientific consensus that synthetic meshes that are low-weight, large-pore, high porosity, monofilament, and capable of maintaining their elasticity under load have better results with fewer complications. Of all mesh characteristics, mesh stiffness, porosity, and pore size are of critical importance.

Synthetic Mesh Use in Pelvic Floor

The TVT-S was cleared for use based on its similarity to predecessor devices, like Ethicon's TVT-Retropubic and TVT-Obturator. During the TVT-R's Food and Drug Administration submission process in the late 1990's, Ethicon used the ProteGen sling as its predicate device. Introduced in April 1997 as a treatment for female SUI, the ProteGen sling was a synthetic polymer (polyester) mesh sling implant—not a polypropylene mesh as in the TVT line of products, including the VT-S. Surgeons implanted the ProteGen polyester sling underneath the urethra to provide support and to reduce SUI. Unfortunately, nearly immediately following ProtoGen's launch, a large number of patients began experiencing

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and vagina. Am J Obstet Gynecol. 2009 May; 200(5):549.e1-8. Costello C, Bachman M, Grand, S, et al. Characterization of heavyweight and lightweight polypropylene prosthetic mesh explants from a single patient. Surg Innov. 2007Sep; 14(3):168-76.

[4] ETH.MESH.00869977; ETH.MESH.02589033; Robinson deposition 7-13, pg. 126-30; Klosterhalfen B, Junge K, Klinge W. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan; 2(1):103-17. Agresta, F, Baldazzi G, Ciardo et al: Lightweight partially absorbable monofilament mesh (polypropylene/poliglecaprone for TAPP inguinal hernia repair. Surg Laparosc Endosc Percutan Tech 2007, 17; 91-94. Amid PK. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia (1997) 1:15-21. Bellon J, Honduvilla N, Jurado F et al: In vitro interaction of bacteria with polypropylene/ePTFE prostheses. Biomaterials. 2001 Jul; 22(14):2021-4. Bouikerrou M, Boulanger L, Rubod C et al: Study of the biomechanical properties of synthetic implanted in vivo. European J. Obstet & Gynecol and Repro Bio 134: (2007)262-267. Klinge U, Klosterhalfen M, Muller A et al: Shrinking of polypropylene mesh in vivo: an experiment study in dogs. European Journal of Surgery Volume 164, Issue 12, pages 965–969, December 1998. Klinge U, Klosterhalfen B, Muller M et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg. 1999 Jul; 165(7):665-73. Klinge U, Klosterhalfen B, Birkenhauer V: Impact of polymer pore size on the interface scar formation in a rat model. J. Surgical Research 103, 208-214 (2002).

severe complications like mesh erosion through the vaginal wall, vaginal infections, vaginal discharge, vaginal bleeding, foul odor, and dyspareunia. In January 1999, Boston Scientific Corporation, ProtoGen's manufacturer, recalled the product due to the unusually high number of complications. In the December 1999 edition of *The Journal of Urology*, a group of respected urologists from across the United States reported their findings on those complications, including a high rate of tissue erosion and urethral erosion.

In November 1998, just months before the ProtoGen recall, Ethicon brought its Tension Free Vaginal Tape (TVT) System to the US market as part of its Gynecare line. The TVT was designed as a pubourethral sling for treatement of female SUI. The device is made from polypropylene mesh (sometimes referred to by the trade name PROLENE). Despite the ProtoGen recall and the two decades worth of literature on the complications resulting from polypropylene mesh implants, the TVT remains on the market today. In fact, Ethicon has expanded the TVT line to include the TVT-O, which incorporates an obturator device to implant the mesh via an "inside-out" approach, and the TVT-S device, which is the primary focus of this report.

Ethicon received FDA approval for the TVT-S device, a single incision sling ("SIS") sometimes referred to as a "mini-sling," in 2005. The sling was composed of approximately 1.1cm x 8.0cm of polypropylene mesh (Prolene) and could be inserted via either the "Hammock approach" or the "U approach." The TVT-S device was removed from the market in 2012, after the FDA requested that Ethicon conduct postmarket surveillance studies. No such studies were performed, and the TVT-S remains off the market to this day.

B. ***The Polypropylene Mesh in the TVT-S Should Not Be Used in the Pelvic Floor Due to Known Complications and Hazards***

Because of the defective characteristics of the TVT-S, as discussed below and throughout this report, Ethicon repeatedly fell below the standard of care in producing and marketing its device. The laser cut mesh used in the TVT-S device should not be used in the pelvic floor, because the risks of the device far outweigh the benefits of the device. The inadequacies of the Prolene mesh and the TVT-S device lead to long term complications, including but not limited to acute and chronic pelvic pain, acute and chronic vaginal pain, permanent dyspareunia, injury and pain to partner during sexual intercourse, sexual dysfunction, chronic infections, abscess formation, permanent nerve damage, defecatory dysfunction, chronic foreign body reaction, lifelong risk of erosion and extrusion, severe vaginal scarring, inability to remove the device, the need for multiple surgical interventions that carry with them significant risks of morbidity, the development of worsening incontinence and urinary dysfunction, including urinary urgency, urinary urge incontinence, and urinary retention. As such, the TVT-S device is not suitable as a permanent implant.

1. <u>The mesh in the TVT-S is not inert and degrades</u>

As polypropylene has been used in surgery for over 50 years as a suture material, Prolene mesh, like the kind used in the TVT-S, was marketed by Ethicon as inert. However, many published studies and internal Ethicon documents show that the mesh is not inert and does in fact degrade.[5] In 1987, for example, Ethicon tested samples of explanted Prolenemesh

[5] ETH. MESH.08315783; ETH.MESH.02589033; Robinson Deposition 7-13, p120, 129-130; Hinoul Deposition 4- 5, p165-170; Kirkemo Deposition 4-18, p138; 84 Klinge U, Klosterhalfen B, Muller M et al: Foreign body reaction to meshes used for the repair of abdominal wall hernias. Eur J Surg. 1999 Jul;165(7):665-73. Klinge U, Klosterhalfen B, Birkenhauer V: Impact of polymer pore size on the interface scar formation in a rat model. J. Surgical Research 103, 208-214 (2002). Klinge U, Klosterhalfen M, Muller A et al: Shrinking of polypropylene mesh in vivo: an experiment study in dogs. European Journal of Surgery Volume 164, Issue 12, pages 965–969, December 1998.; Klosterhalfen B, Klinge W, Schumpelick V: Functional and morphological evaluation of different polypropylene-mesh modifications for abdominal wall repair. Biomaterials. 1998 Dec;19(24):2235-46.; Klosterhalfen B, Klinge W, Hermanns B et al: Pathology of traditional surgical nets for hernia repair after long-term implantation in humans. [ABSTRACT] Chirugr 2000;71:43-51.; Klosterhalfen B, Junge K, Klinge W. The

made from the same material as the TVT-S mesh.[6] After 8 years of implantation, the testing showed that the mesh was severely cracked. In 1992, Ethicon completed a study where Prolene sutures were implanted in beagle dogs for up to seven years. These sutures were removed from the dogs and examined by Ethicon's own scientists, who found surface degradation in many of the samples after 7 years of implantation.[7] Ethicon scientist and corporate spokesperson, Thomas Barbolt, agreed that surface degradation can occur with Prolene mesh, and that this fact was confirmed by the Ethicon studies.[8]

Further evidence that polypropylene mesh degrades over time was provided in 1998 by the publication of the Mary article, who studied the phenomenon of mesh degradation, and concluded the process of polypropylene cooling, where the polypropylene strand cools first on the inside and then on the outside can make the strand more susceptible to degradation on the outside.[9] In 2007, Costello et al., reported that polypropylene is more susceptible to degradation due to oxidation caused by inflammatory response.[10] Using Scanning Electron Microscopy (SEM), degradation could be seen in polypropylene in the form of cracks and peeling.

Dr. Donald Ostergard, urogynecologist and founder of AUGS, created a presentation titled "Polypropylene is Not Inert in the Human Body" in which he described degradation of in vivo polypropylene.[11] Dr. Ostergard concluded that Prolene mesh degradation occurs by oxidation. He further concluded that a large surface area, such a piece of surgical mesh, in

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lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan;2(1):103-17. Clave A, Yahi H, Hammou J, et al. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 patients. Int Urogynecol J. 2010 Mar;21(3):261-70. Klinge et al The Ideal Mesh Klosterhalfen et al: Retrieval study at 623 human mesh explants made ofpolypropylene.

[6] ETH.MESH.12831407

[7] ETH.MESH.05453719

[8] Barbolt deposition, 1-14, p409, 516-517

[9] Mary C, Marios Y, King MW, et al. Comparison of thein vivo behavior of polyvinylidene fluoride and polypropy- lene sutures used in vascular sugary. ASAIO Journal 44, 1998, 199–206.

[10] Costello C, Bachman M, Grand S, et al. Characterization of heavyweight and lightweight polypropylene prostethic mesh explants from a single patient. Surg Innov. 2007 Sep; 14(3):168-76.

[11] "Polypropylene is Not Inert in the Human Body" Presentation by Donald R. Ostergard

contrast to a suture, incites more inflammation and results in more oxidation since more macrophages are present. These macrophages then secrete hydrogen peroxide and hypochlorous acid to oxidize the mesh, which can cause the mesh to become brittle and to crack. As discussed below, these changes cause complications to patients due to the increased inflammatory response.

In a 2010 article by Clave et al., 100 pelvic floor explants were analyzed.[12] Results showed that *all types of polypropylene implants exhibited degradation*. "Mesh damage included superficial degradation, which appeared as a peeling of the fiber surface, transverse cracks in the implant threads, significant cracks with disintegrated surfaces and partially detached material, and superficial or deep flaking." The authors concluded that their research directly "contradicts" the idea that polypropylene is "an inert material." The authors further stated that "[f]or transvaginal surgery, clinical experience indicates the use of low density, large pore implants knitted from a monofilament to facilitate tissue integration, and decrease the inflammatory response…. [N]ot all types of PP implants degraded equally." The authors hypothesized that in vivo oxidation of polypropylene implants, "as reported in the literature," oxidation due to free radical attack, or "septic environment and large detachments of the vaginal approach resulting in collection and bruising hematoma [supporting] both the accumulation of fatty acids and an increased risk of infection," could contribute to degradation. It should be noted that the lead author, Henri Clave, holds an educational position for Ethicon Europe. Two other authors had ties to Sofradim and Covidien.

Later, in 2013, the Wood study found that polypropylene explanted from a patient showed significant oxidation of the material, and concluded that polypropylene will degrade in

[12] Clave A, Yahi H, Hammou J, et al. Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 patients. Int Urogynecol J. 2010 Mar;21(3):261-70.

an oxidizing environment, such as human tissue undergoing a foreign body response.[13] In 2015, seven explants from "Gynemesh, TVT, TOT, SPARC and minisling" were explanted 4-7 years after implantation. Comparison of SEM images for explant samples with control pristine samples revealed extensive surface degradation and the formation of surface cracks in the samples, demonstrating that polypropylene fibers from mid-urethral slings are not inert over time.[14] Other authors and studies have demonstrated similar results with polypropylene in general.[15] Dr. Iakovlev has published numerous articles showing and explaining the degradation and surface cracking of polypropylene explants using histological and transmission electron microscopy approaches.[16]

The fact that polypropylene cracks and breaks inside the human body is a serious concern. As polypropylene degrades, the human body's inflammatory response increases and intensifies. The abraded fiber surface increases the surface area of the mesh, providing multiple areas that can effectively harbor bacteria and become brittle, which lead to an increased risk of an enhanced and chronic inflammatory response, severe scarring, and chronic infections due to bacterial proliferation at the mesh surface.[17]

As stated, Ethicon knew this information decades before the launch of the TVT-S. There are Ethicon studies dating back as far as 1983, using methods nearly identical to Dr.

[13] Wood, et. al. Materials characterization and histological analysis of explanted polypropylene, PTFE, and PET hernia meshes from an individual patient. J Mater Sci: 24:1113-1122 (2013).
[14] K Tzartzeva, D Lingam, M Baniasadi, M Minary-Jolandan, P Zimmern. Neurology and Urodynamics. 2014 33 (6), 820-822.
[15] Iakovlev, et al., Pathology of Explanted Transvaginal Meshes. Intl. Science Index Vol. 8 No. 9 (2014); Martin, MK Gupta, JM Page, F Yu, JM Davidson, SA Guelcher, CL Duvall. Synthesis of a Porous, Biocompatible Tissue Engineering Scaffold Selectively Degraded by Cell-Generated Reactive Oxygen Species. Biomaterials 35(12):3766- 76, 2014; AE Hafeman, KJ Zienkiewicz, AL Zachman, HJ Sung, LB Nanney, JM Davidson, SA Guelcher. Characterization of degradation mechanisms of biodegradable lysine-derived aliphatic polyurethanes. Biomaterials 32(2):419-29, 2011.
[16] Iakovlev V, Guelcher S, Bendavid R. In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades. Virchows Archiv 2014, 463(1): 35; Iakovlev V, Guelcher S, Bendavid R. In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked for Decades. Virchows Archiv 2014, 463(1):35.
[17] Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan;22(1):47-52.

Iakovlev's, showing in vivo degradation of the Prolene polypropylene material.[18] Ethicon conducted additional studies in 1985 (dog study) and in 1987 (human explant), both showing in vivo degradation and cracking of the polypropylene materials.[19] Eventually, Ethicon had its meshes reviewed by an outside consulting company, which found that Ethicon meshes degrade and that the process starts within days of implant.[20]

Remarkably, Ethicon's IFU still claims that the mesh in the TVT-S, "is not absorbed, nor is it subject to degradation or weakening by the action of enzymes."[21] Such a statement is reckless and knowingly false, putting patients at risk for serious complications and leaving physicians without knowledge critical to making informed decisions. It is my opinion, to a reasonable degree of medical and scientific certainty, that polypropylene degrades in the human body, causing complications including but not limited to acute and chronic pelvic pain, acute and chronic vaginal pain, permanent dyspareunia, injury and pain to partner during sexual intercourse, sexual dysfunction, chronic infections, abscess formation, permanent nerve damage, defecatory dysfunction, chronic foreign body reaction, lifelong risk of erosion and extrusion, severe vaginal scarring, inability to remove the device, the need for multiple surgical interventions that carry with them significant risks of morbidity, the development of worsening incontinence and urinary dysfunction, including urinary urgency, urinary urge incontinence, and urinary retention. Undoubtedly, Ethicon should have informed doctors of the known fact of degradation, and the company should have conducted clinical testing relating to the impact of polypropylene degradation in the pelvic floor. Such testing would have

[18] ETH.MESH.15955438
[19] ETH.MESH.00004755; ETH.MESH.11336474; ETH.MESH.13334286
[20] ETH.MESH.07192929
[21] ETH.MESH.02340568

confirmed the fact that polypropylene is not suitable for permanent implantation in the human body.

2. The MSDS for the Prolene mesh states not to use with strong oxiders like peroxides, which can be abundantly found in the vagina

The fact that polypropylene degrades in vivo is especially problematic given the naturally occurring oxidizers in the pelvic floor. Ethicon was warned in advance of the potential consequences of permanently implanting polypropylene in the female body.

The polypropylene mesh in the TVT-S is made from plastic pellets supplied by Sunoco, a petrochemical company. Included with these plastic pellets is a material safety data sheet ("MSDS"), a public document intended to provide those handling or working with the product instructions and information on how to handle the substance in a safe matter, and, more generally, intended to describe the safety (or lack thereof) of a particular product.[22] I have reviewed a number of data sheets for the resin used by various manufacturers to produce pelvic mesh products.

The MSDS for the TVT-S polypropylene states:

> **INCOMPATIBILITY**
>
> The following materials are incompatible with this product: Strong oxidizers such as chlorine, peroxides, chromates, nitric acid, perchlorates, concentrated oxygen, sodium hypochlorite, calcium hypochlorite and permanganates. Chlorine; Nitric acid.[23]

Although the resin used to make the TVT-S mesh is also used in number of other Ethicon products, including Prolene hernia mesh and Prolene sutures, this warning is particularly important as it applies to the TVT-S mesh, as the TVT-S mesh is intended to be placed in the vagina, which is a ready and natural source of peroxides, a strong oxidizer.

[22] Weisberg deposition 8-13, p909.
[23] ETH.MESH.02026591

Peroxides are regularly and naturally produced by a woman's body. By contrast, the Prolene hernia mesh is not intended to be placed in vagina. Further, TVT-S mesh contains approximately 1,000 times more plastic material than a Prolene suture, so the clinical effects of oxidization would be markedly different between a suture and the TVT-S mesh.

This warning in the Prolene MSDS should have triggered an investigation into the effects of naturally occurring oxidizers on the TVT mesh prior to Ethicon's marketing of the device (and certainly prior to the TVT-S, developed years later), particularly with regard to oxidation and degradation of the mesh, as well as inflammation caused the presence of these naturally occurring substances. At the very least, Ethicon should have passed this warning along to surgeons and patients using Prolene mesh, so that they could make an informed choice about whether or not to use the device. However, no such warning regarding the TVT-S mesh's incompatibility with strong oxidizers has been communicated, and Ethicon never did studies specifically examining the clinical effect of these natural oxidizers on the TVT-S mesh. It is my opinion to a reasonable degree of medical certainty that Ethicon has failed in its duty as a reasonable medical device manufacturer by failing to include this warning in the IFU, and by failing to adequately study the clinical effects of the vagina's natural oxidizers on Prolene mesh.

Disturbingly, the MSDS also states that subcutaneous implantation of polypropylene led to local sarcomas in lab rats. The carcinogenic properties of polypropylene also should have been disclosed to doctors, and Ethicon should have done follow-up studies relating to Prolene and cancer. No such disclosure or studies occurred.[24]

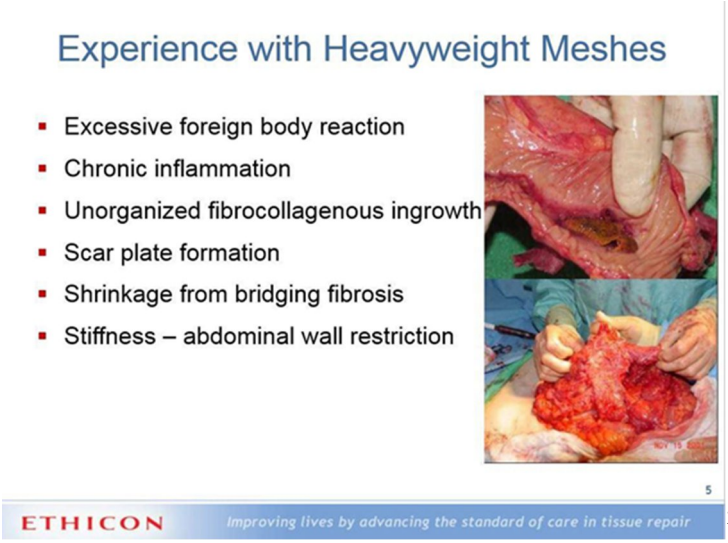
[24] Robinson deposition 9-13, p1105-1115

3. The TVT-S mesh is heavy with small pores, causing increased tissue response, chronic inflammatory response, contraction and shrinkage of the mesh, fibrotic bridging and scar plate formation

Inflammation and Chronic Foreign Body Response

As stated, the Prolene mesh used in devices like the TVT-S is the same mesh Ethicon has used for decades. Ethicon itself refers to the Prolene mesh as "old."[25] Importantly, Ethicon scientists have known for more than 16 years that heavyweight, small pore meshes, like the Prolene mesh comprising the TVT-S, are associated with excessive foreign body reaction, chronic inflammation, bridging fibrosis, scar plate formation, and consequential shrinkage of the mesh.[26] Ethicon knew that the mesh used in the TVT-S is heavyweight and has small pores.[27] Ethicon also knew the need for lighter weight materials, which elicit a lower inflammatory response in the human body.[28]

[25] ETH.MESH.10633520 -22
[26] ETH.MESH.05479411; Klinge U., Klosterhalfen B., Birkenhauer V., Junge K., Conze J., and Schumpelick V., Impact of Polymer Pore Size on the Interface Scar Formation in a Rat Model; Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 2005; 12(1):T1-T7; Cobb, W., et al. Textile Analysis of Heavyweight, Mid-Weight, and Lightweight Polypropylene Mesh in a Porcine Ventral Hernia Model. Journal of Surgical Research 136, 1-7 (2006); Klinge U, Klosterhalfen B, Muller M, Ottinger A, Schumpelick V. Shrinking of Polypropylene Mesh in vivo: An Experimental Study in Dogs. Eur J Surg. 1998: 164; 965-969; Klosterhalfen, B., Junge, K., Klinge, U.The lightweight and large porous mesh concept for hernia repair. Expert Rev. Med. Devices. 2005; 2(1)
[27] ETH.MESH.05479411; ETH.MESH.05479535. Cobb et. al., The Argument for Lightweight Polypropylene Mesh in Hernia Repair, Deposition of Joerg Holste, July 29, 2013 40:12-15, Hellhammer Deposition, 11-13, p151.
[28] ETH.MESH.01203957; ETH.MESH.05479411; Trial Testimony of Piet Hinoul, Batiste, March 27, 2014 afternoon, p73.



[29]

In fact, Ethicon developed lighter weigh materials for use elsewhere in the human body, including the pelvic floor.[30] However, Ethicon continued to use the heavyweight, small pore Prolene mesh, originally developed in 1974 for use in hernia surgery, for its TVT-S device used for SUI.[31] This is true despite the fact that Ethicon knows the heavyweight, small pore meshes cause a greater inflammatory response than lightweight, large pore meshes regardless of where the mesh is located in the human body.[32]

To be sure, the decision to continue using Prolene, despite known complications and the availability of lighter weight, smaller pore mesh, was financial. As Dr. Arnaud put it, Ethicon "want[ed] to be very careful with any modifications of our tape since a change in the mesh would obsolete all the long term clinical results."[33]

The decision to continue using decades-old mesh has had serious ramifications for patients. The body's foreign body response to mesh can cause a chronic inflammatory reaction, leading to excessive scarring in and around the mesh, as well as potentially

[29] ETH.MESH.05479411
[30] Holste deposition 7-13, p51-53.
[31] ETH.MESH.04941016; HMESH_ETH_02030355; ETH.MESH.02340568-ETH.MESH.02340590.
[32] Holste deposition 7-13, p95
[33] ETH.MESH.03911107; Hellhammer deposition, 9-13; Arnaud deposition 7-13, p36-37.

debilitating pain. The degree of this reaction is directly related to the weight and pore size of the mesh device.[34] Ethicon knew that clinical data shows more chronic pain with heavyweight meshes such as the TVT-S mesh, than with lightweight, partially absorbable meshes. One study found that heavyweight meshes with small pores had to be explanted due to chronic pain more frequently than lightweight meshes with large pores.[35] Indeed, Ethicon's own medical director has stated that the presence of the Prolene mesh can be responsible for chronic pain syndrome in the patient.[36]

Shrinkage and Contraction

Further, the foreign body reaction, exacerbated by the heavyweight and small pore construction, is chronic, and this chronic inflammation and reaction can lead to mesh contraction and shrinkage.[37] Most studies show less shrinkage in lighter weight meshes, and pore size is one of the most important factors regarding mesh shrinkage.[38] Ethicon knew that all polypropylene meshes experience a 20-50% reduction in their initial size following implantation in the body.[39] Ethicon's own medical director knew that the Prolene mesh can shrink, and generally believed the TVT mesh would shrink approximately 30% post implantation.[40] The mesh contraction and shrinkage can increase the degree of foreign body reaction and mesh degradation, in turn increasing the degree of pelvic pain and pelvic floor dysfunction, such as dyspareunia and difficulty urinating.[41]

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[34] Hinoul deposition 4-12, p99; ETH.MESH.08315782; Trial Testimony Piet Hinoul, Batiste, March 27, 2014 afternoon, p27; ETH.MESH.05916450
[35] Klostherhalfen,B, Junge, K, Klinge, U, The lightweight and large porous mesh concept for hernia repair. Expert Rev. Med. Devices, 2005 2(1)
[36] ETH.MESH.01202102
[37] Vailhe deposition 6-13, p838.
[38] Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 2005, 12(1):T1-T7.
[39] Cobb W, Kercher K, Heniford T. The Argument for Lightweight Polyropylene Mesh in Hernia Repair. Surgical Innovation. 2005, 12(1):T1-T7.
[40] ETH.MESH.03910418
[41] 41 De Tayrac, et. al. Garcia M, Ruiz V, Godoy A, et al: Differences in polypropylene shrinkage depending on mesh position in an experimental study. American Journal of Surgery Vol 193, Issue 4, April 2007, p538-542.

Additionally, a recent study has shown that mesh shrinkage is progressive, with a linear evolution of the contraction rate over time, indicating that mesh contraction continues in the patient's body indefinitely into the future.[42] Vaginal mesh contraction can result in vaginal fibrosis, infection, chronic vaginal pain, chronic pelvic pain, vaginal shortening, vaginal narrowing, vaginal extrusion, adjacent organ erosion, and dyspareunia. Feiner and Maher evaluated 17 women with vaginal mesh contraction to demonstrate that the mesh caused the condition. The patients' presenting complaints included severe vaginal pain, dyspareunia, and focal tenderness over contracted portions of mesh on vaginal examination, mesh erosion, vaginal tightness, and vaginal shortening. The patients underwent surgical intervention with mobilization of mesh from underlying tissue, division of fixation arms of the central graft, and excision of contracted mesh. Fifteen of 17 (88%) patients reported a substantial reduction in vaginal pain following explanation, while none of 11 (64%) reported substantial reduction in dyspareunia. However, despite Feiner's relative success with mesh explanation, the adverse effects of transvaginal mesh contraction caused permanent life-altering sequelae in 22-46% of patients in this study.[43] I personally see this type of permanent life-altering sequelae in my daily practice in patients I treat for severe complications related to mesh slings, including Ethicon's TVT-S device.

Scarring

Polypropylene induces a rapid and acute inflammatory response and strong scar formation. Heavyweight meshes with small pores, such as the Prolene mesh in the TVT-S, induce an intense, chronic foreign body reaction with intensified fibrotic bridging and scar

[42] Mamy L, Letouzey V, Lavigne J et al: Correlation between shrinkage and infection of implanted synthetic meshes using an animal model of mesh infection. Int Urogynecol J. 2011 Jan;22(1):47-52.
[43] Feiner B, Maher C. Vaginal mesh contraction: definition, clinical presentation, and management. Obstet Gynecol. 2010 Feb;115(2 Pt 1):325-30.; Foon R, Toozs-Hobson P, Latthe P. Adjuvant materials in anterior vaginal wall prolapse surgery: a systematic review of effectiveness and complications. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Dec;19(12):1697-706.

formation.[44] Eventually, the small pores are overwhelmed by the formation of scar tissue, and the entire mesh sling can become encased in a scar plate. This scar plate prevents proper tissue ingrowth.

An increased foreign body reaction with a chronic inflammatory response, followed by the formation of a rigid scar plate, are the primary reasons for the shrinkage and contraction of mesh, which in turn leads to complications including pain and permanent nerve damage.[45] Decreasing the weight of mesh reduces both shrinkage and the inflammatory response. A pore size of at least 1 mm in all directions is needed to prevent the fibrotic bridging and scar plate formation.[46] Despite Ethicon's claims to the contrary, the mesh in the TVT-S has a pore size that is much smaller than 1mm after implantation.[47]

Table 1 - Characteristics of Various mesh implants

MESH	Unit Weight (mg/cm2) permanent component	Burst Strength, psi	Maximum Pore Size, mm
PROLENE* Polypropylene Mesh	7.6	234	<1
GYNECARE GYNEMESH* PS Nonabsorbable (PROLENE* Soft Mesh)	4.5	116	2.5
MERSILENE* Polyester Fiber Mesh	3.3	83	<1
VYPRO Mesh	2.5	71 (pre-absorption 90)	4.5
VYPROII Mesh	3.5		3-4
ULTRAPRO* Partially Absorbable Mesh (GYNECARE GYNEMESH M* Mesh)	2.8	90 (pre-absorption 135)	5.0

[48]

[44] ETH.MESH.02316781; ETH.MESH.01218361
[45] ETH.MESH.01218361
[46] ETH.MESH.01785259; ETH.MESH.02316781; ETH.MESH.02148431; ETH.MESH.01218361; Klosterhalfen B, Junge K, Klinge U. The lightweight and large porous mesh concepts for hernia repair. Expert Rev Med Devices. 2005 Jan;2(1):103-17; Batke deposition 8-12, p113-114, 118-120, 172-174;Hellhammer deposition 9-13, p403-407; Holste deposition 7-13, p51-53; Holste Deposition 12-12, p89-90; Semin Immunopathol (2011) 33:235–243 - a Scar net formation following large pore (~3 mm) and b scar plate formation following small-pore (~0.3 mm) mesh implantation; Arnaud deposition 9-13, p756-757; ETH.MESH.03021946; ETH.MESH.02587926; ETH.MESH.01752532; ETH.MESH.01785259; ETH.MESH.04941016
[47] ETH.MESH.08315782
[48] ETH.MESH.08315782

The fact that the pore size of the TVT-S is not greater than 1mm in all directions prevents proper tissue integration, which can reasonably be expected to result in the development of a rigid scar plate, leading to, among other things, the potential for increased erosion, pain, nerve entrapment, vaginal shortening, SUI recurrence, urethral obstruction, and dyspareunia.[49] As with other risks, it is well-documented that Ethicon also knew the design of its Prolene mesh could lead to a severe foreign body reaction, excessive scarring and fibrotic bridging, and mesh shrinkage.[50] Nonetheless, Ethicon failed to disclose its own findings, leaving doctors and patients in the dark.

4. Ethicon's Prolene mesh tested positive for cytotoxicity

Cytotoxicity is the quality of being toxic to cells. If a woman's tissues or organs are exposed to a cytotoxic substance, the cells may experience necrosis and die rapidly, or they may undergo a form of controlled cell death known as apoptosis. It is my understanding that it is common for medical devices to be subjected to cytotoxicity testing before they are marketed to doctors and patients.

In support of its application to market the TVT (and then the TVT-S) in the United States, Ethicon did not perform any controlled clinical studies to determine the cytotoxic potential of the TVT, but instead determined that the "long term clinical experience with PROLENE mesh indicated the [prior] cytotoxicity testing would be sufficient to support the biocompatibility of this [mesh] component."[51] Of course, prior to marketing the TVT device, the Prolene mesh had primarily been used in abdominal hernia repair, and had never before been specifically indicated for use in vaginal tissues. As a result, Ethicon's conclusion that no

[49] Klinge U, Otto J, Muhl T. High Structural Stability of Textile Implants Prevents Pore Collapse and Preserves Effective Porosity at Strain. BioMed Research International. 2015, 953209.
[50] ETH.MESH.05920616; ETH.MESH.04037600; ETH.MESH.05920616; ETH.MESH.05585033; ETH.MESH.05446127; ETH.MESH.05475773; ETH.MESH.04015102; ETH.MESH.04037600; Batke deposition 8-13, p87-88, 113-114, 257-259; Holste deposition 7-13, p51-57; Vailhe deposition 6-13, 182-185.
[51] ETH.MESH.08476210

new clinical or animal studies were needed to evaluate the cytotoxic potential of the TVT mesh is questionable at best. In fact, to this day, I am not aware of any long-term studies undertaken by Ethicon to determine whether or not the TVT mesh is clinically cytotoxic in women.[52]

Notably, the 2004 Wang study reported a defective healing rate of 2.2% in a series of 670 patients, and a persistent defective healing rate of 1%, which is suggestive of cytotoxicity.[53] Although this study was not published until 2004, Ethicon had been advised that Dr. Wang had experienced 25 erosions from the TVT mesh, which he suspected was due to the body's rejection of the Prolene mesh in 2002.[54]

The initial Cytotoxicity testing of the TVT prototype device was conducted in March of 1997, and tested all components of the device together for a period of 24 hours. The results of this test indicated the mesh was severely cytotoxic.[55] Ethicon's own Scotland lab performed follow-up testing, this time testing the needle, heat shrinking tube, sheath, and polypropylene mesh separately. In this test, the polypropylene mesh in the TVT again tested positive for marked cytotoxicity. Ethicon did a third and final test in July of 1997, which finally provided a non- cytotoxic result for the polypropylene mesh. Ethicon relied on the results of this final, July 1997 test in support of its application to market the TVT device, and did not report the two prior positive cytotoxic test results to the FDA, surgeons, or the public.

Ethicon's own Worldwide Medical Director from 2005-2010 was not aware of these positive tests during his tenure.[56] Notably, even the 1997 ISO elution testing showed that the polypropylene mesh in the TVT was moderate to severely cytotoxic, while the ISO agarose

[52] Robinson deposition 9-13, p1101-1102.
[53] Wang AC, et. al. A histologic and immunohistochemical analysis of defective vaginal tape healing after continence taping procedures: A prospective case-controlled pilot study. American Journal of Obstetrics & Gynecology. 2004;191(6):1868–1874.
[54] ETH.MESH.03736989; ETH.MESH.00409674
[55] ETH.MESH.06851860
[56] Robinson deposition 9-13, p1094-1095.

diffusion testing showed the mesh was non-cytotoxic. Despite the positive ISO elution testing, and the two previous tests showing the mesh was cytotoxic, Ethicon concluded that "the long history of safe clinical use of polypropylene as a mesh and suture products suggests strongly that the material is inherently biocompatible, and the potential cytotoxicity observed is self-limiting and minimal when compared to the implantation procedure itself."[57]

It is my opinion that based on the 3 positive cytotoxic test results, Ethicon failed in its duty as a reasonable medical device manufacturer by not conducting long-term studies to assess the cytotoxic potential of the TVT mesh, and thus the TVT-S mesh, prior to marketing the device in women. This is particularly true in light of the fact that the Prolene mesh had never before been indicated specifically for use in vaginal tissues, and that there was only limited, short term data for 200 patients on a prototype device available at the time the device was first sold in the United States. In addition, the reports of 25 tape erosions from Dr. Wang in 2002 should have triggered an additional testing and assessment of the cytotoxic potential of the TVT mesh, but no additional cytotoxic testing was done as a result of these reports.

Although Ethicon claims to have conducted additional cytotoxicity testing prior to FDA approval of the TVT-S, this does not explain the prior positive tests relating to the TVT.[58] And, given the company's history of selectively releasing studies and tests, the 510(k) application hardly puts to rest concerns about Prolene's cytotoxic nature.[59] I have personally

[57] ETH.MESH.08476210

[58] ETH.MESH.01311841

[59] Ethicon has never conducted a long-term randomized controlled trial with safety as a primary endpoint. (Trial Testimony of Piet Hinoul, Batiste, March 27, 2014 afternoon, p57.) In addition, to my knowledge, with respect to studies performed by persons outside of Ethicon, very few are long term randomized controlled studies and none include a primary endpoint of safety. (Robinson deposition 9-13, p977.) There have also been recent studies that suggest that the studies assessing risks of synthetic mid-urethral slings to date are poor and that long term data or evidence lags behind shorter-term studies. (Ford, et. al. Mid-urethral sling operations for stress urinary incontinence in women (review). The Cochrane Library (2015); Blaivas, et. al. Safety considerations for synthetic sling surgery. Nat. Rev. Urol. 2015:12 481-509.) Ethicon routinely relies and promotes its products based on long-term data from the original Ulmsten (and later Nilsson) data and studies. However, the studies lack significant data and fail to consider or inquire about many safety risks on the original patient cohort. The Ulmsten/Nilsson data is also biased in that Dr. Ulmsten had financial incentives to obtain certain results with his original studies and received numerous payments,

seen the clinical effects of the cytotoxic potential of Prolene mesh in my practice. When I have removed Prolene TVT-S mesh from a patient with a mesh erosion, the tissue surrounding the mesh frequently shows evidence of necrosis and cell death. This type of necrosis is typically due to either toxins, infections, trauma, or some combination of the three.

C. ***The TVT-S Should Not Be Used in the Pelvic Floor Due to its Defective Design***

1. The TVT-S mesh is laser cut, resulting in a stiffer product and higher incidence of complications

Originally, Ethicon produced its line of TVT products by mechanically cutting the Prolene mesh. With the introduction of TVT-S, the company decided to use lasers to cut the mesh instead of machines. According to Ethicon, the change to lasers meant that the new mesh "was about three times stiffer than the machine-cut TVT mesh."[60]

Predictably, Ethicon conducted no clinical testing on the significance between mechanical cut and laser cut mesh.[61] According to internal Ethicon documents, the company tried to stress that there was nothing clinically significant or "new" about laser cut mesh, in part because "[I]f our results are as we claim [then] why are we changing the mesh with no clinical data?"[62]

Most importantly, the stiffness of the laser-cut mesh can result in additional complications for the patient, as compared to mechanically cut mesh. According to multiple Ethicon employees, for example, stiffer or more rigid mesh can result in a higher incidence of erosion, sexual dysfunction, and voiding dysfunction.[63] A study by Neuman found much

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consulting agreements, and royalties related to the TVT and his involvement with Ethicon. (ETH.MESH.03259439; Robinson deposition 9-13, p214-219.)

[60] ETH.MESH.01809080; Moalli P. A., Papas N., Menefee S., Albo M., Meyn L., Abramowitch S. D. Tensile properties of five commonly used mid-urethral slings relative to the TVT. International Urogynecology Journal and Pelvic Floor Dysfunction. 2008;19(5):655–663.

[61] ETH.MESH.01221735; ETH.MESH.03941617

[62] ETH.MESH.06040171

[63] ETH.MESH.00294195; ETH.MESH.00271641; ETH.MESH.00328895; ETH.MESH.03916716; ETH.MESH.01782949

higher rates of dyspareunia, attributable to the stiffness of the mesh.[64] In my own practice, I have likewise noticed the more rigid quality of mechanically cut mesh and have identified these types of complications following implantation.

2. The TVT-S design is flawed because there is no way to properly tension the device

Proper tensioning of the TVT-S device is critical to ensure that the device is both successful in its intended use to cure stress urinary incontinence and to prevent complications. However, the design of the TVT-S device is flawed because Ethicon cannot properly determine and/or instruct surgeons on the proper placement of the device and, in fact, Ethicon provides nonsensical or misleading instructions on tensioning in its Instructions for Use ("IFU"). It is known that improper tensioning of slings can lead to failure of the procedure, urinary retention, and well as urinary obstruction. The TVT-S IFU itself states that "[o]ver-correction, i.e., too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction," and that "[u]nder-correction . . . may result in incomplete or no relief from urinary incontinence."[65] Too much tension on the mesh can also lead to vaginal or urethral erosions, which the IFU does not mention.[66]

To begin with, the IFU repeatedly refers to the TVT-S as "tension free." And yet the IFU warns that "over-correction, i.e., too much tension" can result in complications. Presumably, if the tape is "tension free," the IFU should state that *any* tension can result in complications, not merely the vague phrase "too much." Worse, the IFU warns of the possibility of "under- correction," which is presumably impossible with a device that is truly tension free. The IFU informs surgeons to "[e]nsure that the tape is placed with no tension."

[64] Neuman M. Transobturator vs. Single-Incision Suburethral Mini-slings for Treatment of Female Stress Urinary Incontinence: Early Postoperative Pain and 3-year Follow Up. J Min. Invas. Gynecol 2011 Nov-Dec;18(6):769-73.
[65] ETH.MESH.02340589
[66] ETH.MESH.05529653; ETH.MESH.0016113; ETH.MESH.05529274; ETH.MESH.04044797

I am not alone in my confusion regarding the tensioning of the TVT-S. Key Opinion Leader Malcolm Frazer reported to Ethicon in November 2007 that "the [TVT-S] IFU is fundamentally misleading. Tension-free, tension-less and placement with no tension are complete misnomers."[67] Professor Frazer also noted that Ethicon "is now suggesting [outside the IFU] that [the TVT-S] should be much tighter than [the IFU] states, because you assume [the mesh] or tissues may loosen." (Other Ethicon documents include similar suggestions regarding additional tension.)[68] He further stated that Ethicon had released "inadequate" and "contradictory or confusing statements on tension."

The IFU also instructs that the procedure may be performed under general anesthesia. However, the IFU notes that the positioning of the "tension-free tape" should be considered by "cough test or other [undescribed] means." It is impossible to perform a cough test with a patient under general anesthesia, and Ethicon quite literally provides no guidance for assessing the placement and tensioning of the TVT-S in that situation.

Ethicon's lack of guidance on tensioning the TVT-S is a repeat of the company's approach to the original TVT. For example, the fact that the cough test was necessary to properly tension the mesh was noted by Dr. Ulmsten in his original 1996 publication on the TVT, as well as the co-inventor of the TVT, professor Nilsson, who noted that there was a 15% difference in success rates between patients treated with the TVT under local anesthesia with a cough test, and patients under general anesthesia, where no cough test was possible.[69] Despite being aware of this concern, Ethicon launched the TVT with an IFU that informed physicians that the procedure could be performed under general or local anesthesia, yet did not inform physicians that the success rate was much greater if performed under local anesthesia

[67] ETH.MESH.00311792
[68] ETH.MESH.01782949
[69] ETH.MESH.0404851

with a cough test. In 2001, Ethicon medical directors recognized the need to have a standardized approach for tensioning the TVT and began work on a product which would avoid excessive tension. This product was never completed, and Ethicon never addressed how to instruct surgeons to properly tension the mesh. Ethicon employees have acknowledged that the TVT line has never truly been tension free, despite years of marketing it as such, and that they cannot accurately describe how to tension the mesh.[70]

Further, the fact that the mesh undergoes changes to its physical characteristics, which may vary from patient to patient, within days of implantation and then continuously throughout its time in the human body, means that "proper" tensioning is likely impossible. Ethicon failed to consider or inform physicians that the mesh could shrink from 30-50% once the TVT-S was placed, which obviously affects the final placement and tensioning of the mesh.[71] (Actual shrinkage rates vary based on the individual patient, type of mesh, and location of mesh in the body.)

In sum, Ethicon's instructions leave the physician with no clear, articulable standard on how to avoid serious adverse reactions like urinary retention or urinary obstruction. Since it is generally impossible to adjust the tensioning more than 24 hours after an operation due to tissue ingrowth, a re-operation surgery is generally required to correct improper tensioning. Therefore, it is particularly important to describe the proper tensioning of the device as part of the product information.

It is my opinion to a reasonable degree of medical certainty that Ethicon has failed in its duty as a reasonable medical device manufacturer by not developing and articulating clear and accurate instructions to surgeons on how to tension the mesh, rendering the device defective. It

[70] ETH.MESH.01784428; ETH.MESH.06861473
[71] ETH.MESH.03917375

is also my opinion to a reasonable degree of medical certainty that Ethicon cannot develop and articulate clear and accurate instructions on how to properly tension the mesh as long as defects of heavyweight, small pore, polypropylene mesh exist, as those defects create too many variations in the tensioning of the device to be overcome by instructions, no matter how well designed and articulated they may be.

3. The TVT-S is defectively designed in its insertion instruments and technique

Like the TVT and TVT-O, the design of the TVT-S is inherently defective given its use of Prolene mesh, which degrades and deforms in the pelvic floor, leading to serious complications as explained above. The TVT-S, moreover, was in fact designed even more poorly than its predicate devices.

Ethicon received FDA approval for the TVT-S under the 510(k) approval process, which is meant for devices that are "substantially equivalent" to a previously approved device. Ethicon asserted that the TVT-S was substantially equivalent to the TVT and TVT-O, but the reality is that the TVT-S is quite different, particularly as far as the implantation technique. The inserters were new,[72] and the procedure, including the "hammock" and "U" methods, was new.[73] As stated previously, the mesh was also the first to be laser cut, which alters the physical characteristics of the mesh as compared to the mechanical cutting utilized for the TVT. As Malcom Frazer put it: the TVT Secur is so "utterly different to the other TVT's that it probably shouldn't be called a TVT."[74] Similarly, Dr. Menachem Neuman, who flew across Europe providing training sessions for Ethicon products, informed the company that "special awareness" should be paid "to the differences between the TVT/TVTO and the TVTS . . . if

[72] Robinson deposition 7-13, p116.
[73] ETH.MESH.17666960; ETH.MESH.02340577
[74] ETH.MESH.00327062

high cure rates and low complication rates are desired."[75] (Dr. Neuman provided a number of suggestions regarding TVT-S techniques, none of which were used in an amended IFU.)

The primary problems with the TVT-S, as compared to the predecessor devices, are the insertion tools and techniques. Throughout the TVT-S's time on the market, Ethicon was aware of complaints relating to difficulty removing the insertion device.[76] For example, in a 2006 email to David Robinson and Dan Smith, among others, Ethicon's Director of Risk Management Mark Yale described the "potential high rate of occurrence with injuries related to [the TVT-S] not coming off inserter during removal of the inserter, therefore the device is either moved from rest position or completely pulled out along with inserter."[77] A Quality Board presentation likewise noted complaints regarding the inserter clinging to the device.[78]

The various problems and potential explanations were summed up in a study by Hota:

> The lower overall success of TVT-S could be attributed to the difficulty that was sometimes encountered in the detachment of the introducer from the sling. During the introducer removal process, the original tensioning may have been compromised, as the introducer was moved back and forth in an attempt to release the sling from the introducer….
>
> Another point to consider is that the ends of the TVT-S are intended to be embedded within the obturator internus muscle, as opposed to passing through the obturator membrane as with the TVT-O sling. The TVT-S may theoretically migrate with time, detaching from the obturator internus muscle, whereas with TVT- O, the mesh passes through the obturator membrane as well as the obturator internus and externus muscles and the adductor magnus muscle and therefore may not be dislodged as easily. In other words, the latter approach may create a more reliable anchor for the mesh. In addition, excessive hydrodissection or sharp dissection of the periurethral space may affect the degree of attachment of the absorbable "fleece" on either end of the TVT-S. In addition, the attachment of the fleece could be compromised

[75] ETH.MESH.02320486
[76] ETH.MESH.02105223; ETH.MESH.03752501
[77] ETH.MESH.0329316
[78] ETH.MESH.06051286

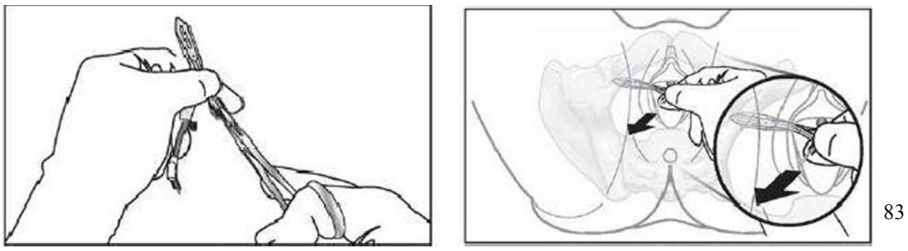
> if a hematoma developed within the obturator internus muscle as a result of the surgical procedure.[79]

The "fleece" material is identified by Ethicon as a combination of polyglactin 910 and poly-p-dioxanone.[80] It was not used in either the TVT or TVT-O, and to my knowledge Ethicon did not perform any studies regarding its use in the pelvic floor. The TVT-S should not have launched without clinical findings showing that the new absorbable materials did not hamper insertion or integration of the device.

Another issue with the TVT-S insertion tools are the razor-sharp edges on the steel inserters. The Hota study found "an increased incidence of mesh exposure in the TVT-S group," and theorized that "the sharper edges of the TVT-S introducer potentially create more trauma to the vaginal epithelium and may result in high erosion rates." A "high-quality review . . . conducted to pool relevant data from randomised controlled trials" is consistent with these findings.[81] The report found that the TVT-S resulted in both more frequent vaginal exposure of mesh and mesh extrusion into the bladder or urethra, as compared to TVT-O-like devices. The TVT-S procedure also made women lose more blood than the TVT-O procedure—a statistically significant amount. Consistent with other studies, the report determined that failure rates among single-incision slings were also higher than with the transobturator approach.[82] The study concluded that "TVT-Secur is inferior to TVT and has already been withdrawn from clinical use." Once again, Ethicon did not study the potential effects of its razor-sharp instruments. The TVT-S never should have been released with this component; whatever benefits of this razor- sharp tool were clearly outweighed by the risks. It is my opinion that the

[79] Hota, Lekha S., MD, et al. TVT-Secur (Hammock) Versus TVT-Obturator: A Randomized Trial of Suburethral Sling Operative Procedures. Female Pelvic Med Reconstr. Surg. 2012, Jan-Feb;18(1):41-45.
[80] ETH.MESH.02340577
[81] Nambiar A, Cody JD, Jeffery ST. Single-incision sling operations for urinary incontinence in women (Review). The Cochrane Library, 2014, Issue 6.
[82] Maslow K, Gupta C. Randomized clinical trial comparing TVT Secur system and transvaginal obturator tape for the surgical management of stress urinary incontinence. Int Urogynecol J (2014) 25:909–914.

sharp edges of the inserter are more likely to cause injuries to tissue and more likely to result in mesh erosion and extrusion.

 [83]

4. There are safer, feasible alternatives to the TVT-S Prolene mesh that would have reduced or eliminated many of the risks to patients in whom the TVT-S device has been implanted

It is my opinion, to a reasonable degree of medical certainty, that using an alternative product like a suture product, as with the Burch procedure, or using a pubovaginal sling (autologous, cadaveric or xenograft) or an allograft sling, like Repliform, or a different synthetic material, instead of the Prolene polypropylene mesh used in TVT-S, would have been safer, feasible alternatives that would have reduced the risk of the injuries suffered by women as a result of the defective TVT-S. A different suture material, a pubovaginal sling, an allograft sling or sutures used in an alternative design to the TVT-S, would reduce the risk of fibrotic bridging and mesh encapsulation, mesh contraction, mesh degradation, mesh hardening/rigidity, mesh curling/roping/fraying/deformation, mesh pore collapse/deformation at minimal stress, and chronic inflammation and chronic foreign body reaction of the TVT-S.

It is my further opinion to a reasonable degree of medical certainty that a shorter, lighter weight, larger pore mesh sling with less Prolene material (e.g., Ultrapro) would have been a safer, feasible alternative design and would have reduced the risk of the injuries suffered by women from the defective TVT-S. A lighter weight, larger pore mesh (e.g., Ultrapro) would reduce the risk of fibrotic bridging and mesh encapsulation, mesh contraction, mesh

[83] ETH.MESH.02340568

degradation, mesh hardening/rigidity, mesh curling/roping/fraying/deformation, mesh pore collapse/deformation at minimal stress, and chronic inflammation and chronic foreign body reaction of the TVT-S.

In general, the best course of action is to avoid using polypropylene mesh in the pelvic floor. Traditional non-surgical repairs are often helpful, and traditional surgical repairs have similar success rates as devices like the TVT, with far fewer complications. Even so, feasible, safer, cost-effective, alternative devices were available to Ethicon at the time the TVT-S was launched and throughout the period it was marketed. As documented in the scientific literature and in Ethicon's internal communications, the TVT and TVT-O had far better success rates than the TVT-S.[84] Further, Ethicon developed (and used in its POP kits) the lightweight, large pore Ultrapro mesh, but chose not to utilize it in any treatment for SUI.[85] Any or all of these readily available options would have resulted in a more successful device with fewer complications and better outcomes.

D. ***Ethicon Failed to Disclose and/or Downplayed Adverse Risks, Complications, and Product Information in its Instructions for Use ("IFU") and Patient Brochures***

It is important to state from the outset that Ethicon released one set of Instructions for Use ("IFU") for the TVT-S and never updated it, even as the company received more and more complaints from users and documents show growing concerns within the company itself. From launch, Ethicon's IFU failed to disclose important safety and risk information to physicians, thereby compromising the ability for all levels of surgeons to adequately and appropriately inform their patients prior to the implantation of the TVT device.

[84] ETH.MESH.00312179; ETH.MESH.03845446; ETH.MESH.02105223; ETH.MESH.03845446; Nambiar A, Cody JD, Jeffery ST. Single-incision sling operations for urinary incontinence in women (Review). The Cochrane Library, 2014, Issue 6.
[85] Hellhammer deposition 9-13.

The IFU serves as the main modality for information regarding surgery. The IFU is the one document that Ethicon knew all surgeons see prior to the implantation of a mesh device.[86] In addition, according to Ethicon's Medical Director Piet Hinoul, physicians should be allowed to rely on the safety information in the IFU standing alone.[87] Thus, all risks associated with a medical device must be included in the products' IFU,[88] so that doctors are not left in the dark. I regularly review and rely on IFUs in my on practice. The woefully inadequate IFU for the TVT- S lists the following information in its Adverse Risks Section:

- Punctures or lacerations or injury to vessels, nerves, bladder, urethra, or bowel may occur during instrument passage and may require surgical repair.
- Transitory local irritation at the wound site and a transitory foreign body response may occur. This response could result in extrusion, erosion, fistula formation or inflammation.
- As with all foreign bodies and surgical implants, PROLENE mesh and absorbable materials may potentiate or exacerbate an existing infection.
- Over-correction, i.e., too much tension applied to the tape, may cause temporary or permanent lower urinary tract obstruction.
- Under-correction or incorrect placement may result in incomplete or no relief from urinary incontinence.[89]

This is a nearly word-for-word recitation of the Adverse Reactions listed in the early 2000s TVT IFUs, even though, as explained, the products are quite different.[90] By contrast, the

[86] Isenberg deposition 11-13, p566.
[87] Hinoul deposition 1-14, p1207-1208
[88] Beath deposition 7-12, p592; Weisberg deposition 8-13, p959-960.
[89] ETH.MESH.02340589
[90] ETH.MESH.05225354

current version of the TVT IFU, although still flawed in many ways, lists the following Adverse Reactions:

- Punctures or lacerations of vessels, nerves, structures or organs, including the bladder, urethra or bowel, may occur and may require surgical repair.
- Transitory local irritation at the wound site may occur.
- As with any implant, a foreign body response may occur. This response could result in extrusion, erosion, exposure, fistula formation and/or inflammation.
- Mesh extrusion, exposure, or erosion into the vagina or other structures or organs.
- As with all surgical procedures, there is a risk of infection. As with all foreign bodies, PROLENE Mesh may potentiate an existing infection.
- Over correction, i.e., too much tension applied to the tape may cause temporary or permanent lower urinary tract obstruction.
- Acute and/or chronic pain
- Voiding dysfunction
- Pain with intercourse which in some patients may not resolve.
- Neuromuscular problems, including acute and/or chronic pain in the groin, thigh, leg, pelvic and/or abdominal area may occur.
- Recurrence of incontinence
- Bleeding including hemorrhage, or hematoma.
- One or more revision surgeries may be necessary to treat these adverse reactions.
- PROLENE Mesh is a permanent implant that integrates into the tissue. In cases in which the PROLENE Mesh needs to be removed in part or whole, significant dissection may be required.

OTHER ADVERSE REACTIONS

- Seroma
- Urge incontinence
- Urinary frequency
- Urinary retention
- Adhesion formation
- Atypical vaginal discharge
- Exposed mesh may cause pain or discomfort to the patient's partner during intercourse.
- Death.[91]

As explained throughout this report and described in more detail below, the IFU for the TVT-S fails to disclose numerous adverse risks, safety information, and warnings that were well- known to Ethicon while the TVT-S was being marketed. Most strikingly, the IFU fails to mention pelvic pain or dyspareunia, which are extremely common complications of mesh implantation. More specifically, the TVT-S IFU fails to warn doctors of the known risks of, among other things: death, acute and chronic pelvic pain, acute and chronic vaginal pain, permanent dyspareunia, injury and pain to partner during sexual intercourse, sexual dysfunction, chronic infections, abscess formation, permanent nerve damage, defecatory dysfunction, chronic foreign body reaction, lifelong risk of erosion and extrusion, severe vaginal scarring, inability to remove the device, the need for multiple surgical interventions that carry with them significant risks of morbidity, the development of worsening incontinence and urinary dysfunction, including urinary urgency, urinary urge incontinence, and urinary retention. The IFU also fails to mention, among other things, the research showing that

[91] TVT IFU (01/2015), available at http://hostedvl106.quosavl.com/qb/doc/0nnlfm86hbpkf33bt7pl38flvg

polypropylene is carcinogenic and that Prolene is cytotoxic. And the IFU omits any mention of the fact that Prolene mesh is known to degrade, contract, and shrink.

As described throughout this report, my review of internal documents and the depositions of Ethicon employees reveals that Ethicon was aware of each these risks before or at the time the TVT-S was first marketed and sold.[92] In my opinion, Ethicon's failure to warn of these significant risks resulted in injuries to many women.

Ethicon also failed to include warnings in its IFU related to the increased risk of mesh extrusion in women with prior vaginal surgeries, vaginal atrophy, vaginal injury, and post-operative infection.[93] In addition, Ethicon failed to inform physicians that the TVT-S procedure performed under general anesthesia increases the risk of urinary retention, erosions, and failure of the surgery. Ethicon also failed to mention the risks associated with its new razor-sharp insertor and increased risk of certain complications relating to laser cut mesh. Finally, Ethicon did not tell physicians that the TVT-S device would not work as well in smokers or obese patients.[94] All of these risks should have been disclosed to every surgeon via the original TVT-S IFU. It is inexcusable that no amendment was made to the IFU throughout the TVT-S's marketing period.

In addition to omitting information, Ethicon also downplays and misrepresents significant information in its IFU related to certain mesh properties. For example, despite the significant amount of data regarding mesh-related inflammatory response, the IFU for TVT-S states, "Transitory local irritation at the wound site and a transitory foreign body response may occur." According to the scientific literature, my own clinical experience, deposition testimony

[92] Hinoul deposition 6-13, p552; Beath deposition 7-13, p608; Robinson deposition 7-13, p251; ETH.MESH.00312180; ETH.MESH.04081189; ETH.MESH.02089392; ETH.MESH.04099233; ETH.MESH.03910175
[93] Isenberg deposition 11-13, p582-583, ETH.MESH.00159634; ETH.MESH.00203456
[94] ETH.MESH.00640394, Kirkemo deposition 1-14, p556-558.

of Ethicon employees, and Ethicon's internal documents, the foreign body response is far from "transitory."[95] As Ethicon's Associate Medical Director of Worldwide Customer Quality explained, "[F]rom what I see each day, these patient experiences are not 'transitory' at all."[96] Notably, the word "transient" no longer modifies "foreign body response" in the latest TVT IFU. Further, Ethicon states in its IFU that the polypropylene mesh is not subject to degradation, which is inconsistent with Ethicon's own internal findings, as described in detail above.

In short, Ethicon not only failed to disclose certain risks associated with the product, it downplayed or inaccurately portrayed known issues related to mesh implantation. Thus, Ethicon prevented physicians from having an appropriate and accurate informed consent discussion with their patients by concealing and misrepresenting this type of information. The information Ethicon provided in patient brochures was no better, similarly downplaying risks, omitting safety information, and improperly equating the TVT-S with the TVT, as though the risks and benefits were the same. [97] As a result, numerous patients have suffered injuries from the TVT-S device that might have been avoided.

E. ***Ethicon Failed to Provide Adequate Training for Surgeons Using the TVT-S***

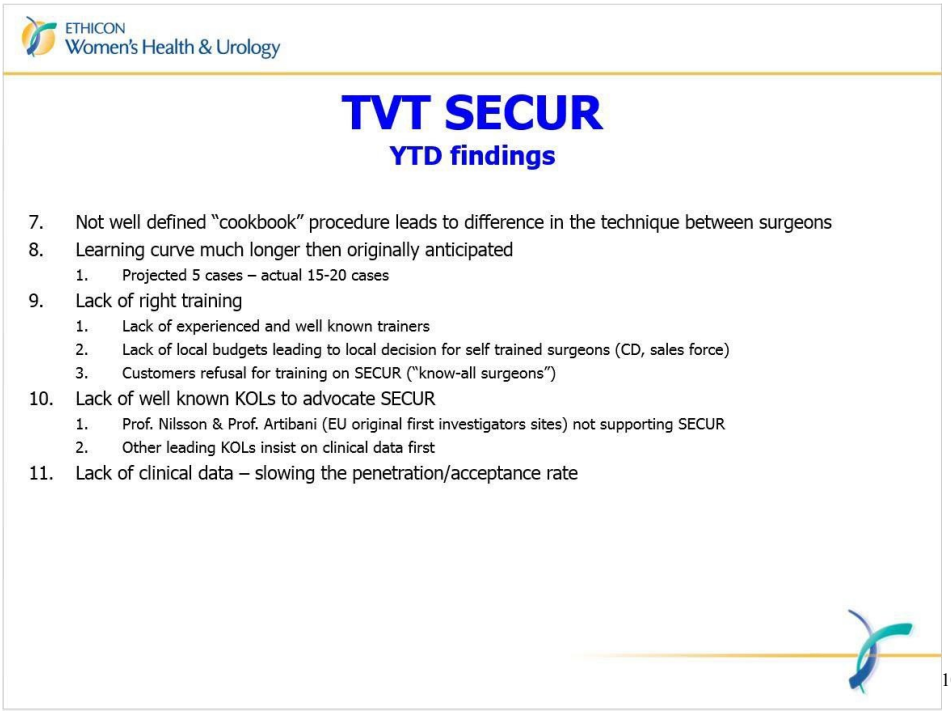
As explained above, the implantation of the TVT-S device was a very different experience for surgeons compared to the TVT and TVT-O. Unfortunately, Ethicon left them in the dark.

For example, in addition to the tension and inserter issues described in this report, Ethicon did not provide surgeons with accurate information regarding the incision size for

[95] Robinson deposition 9-13, p1087-1089; Hinoul deposition, 1-14, p1192-1199.
[96] ETH.MESH.04093125
[97] ETH.MESH.08003263; ETH.MESH.08003279

implantation. The IFU states that the incision size should be 1.0-1.5 cm.[98] But Dr. Arnaud's "cookbook"[99] and "procedural pearls"[100] suggested a larger incision size, in order to reduce the risk of erosion or exposure.[101] The new size was larger than what was required with older slings.[102]

According to their own documents, Ethicon employees were well-aware that surgeons were struggling.[103]



[104]

Even Ethicon KOLs needed dozens of surgeries before they became something close to proficient in utilizing the TVT-S.[105]

[98] ETH.MESH.02340568
[99] ETH.MESH.03752501; ETH.MESH.00519476
[100] ETH.MESH.07039973
[101] ETH.MESH.17666960
[102] ETH.MESH.17666960
[103] ETH.MESH.0324086; ETH.MESH.0329557; ETH.MESH.00330141; ETH.MESH.03922618; ETH.MESH.00874445; ETH.MESH.00642325; ETH.MESH.02105223; ETH.MESH.03845446; ETH.MESH.01784428; ETH.MESH.03752501
[104] ETH.MESH.02105223
[105] ETH.MESH.02105223; ETH.MESH.03845446; ETH.MESH.04048515

It is my opinion to a reasonable degree of medical certainty that Ethicon should not have launched the TVT-S without better instructions, and should have provided better training to all surgeons. This issue might have been avoided with extensive pre-launch clinical studies, but none were performed.[106] Internal Ethicon documents suggest that the company continued to market the product as something that could be easily implanted, for fear of losing market share.[107]

V. Conclusion

In sum, I concur with the results of Ethicon's (unpublished) summary of first-year data on the TVT-S, which showed that nearly a third of women experienced "major" complications: "As long as complications occur at the rate seen in this study . . . the single-incision procedure cannot be recommended as a first line treatment for [SUI]."[108] As explained throughout this report, the TVT-S is a defective device sold with faulty instructions, which never should have been brought to market. As a result of the TVT-S, many women have experienced severe complications that are in many cases irreversible.

05/22/17
DATE

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[106] ETH.MESH.00134795
[107] ETH.MESH.00858636
[108] ETH.MESH.02916611